R E M A R K S

The previous Office Action of October 17, 2003 enclosed copies of the INFORMATION DISCLOSURE STATEMENTS BY APPLICANT Form PTO-1449 dated May 25, 2001; Form PTO-1449 dated June 11, 2001; and Forms PTO/SB/08A and PTO/SB/08B dated August 2, 2002, with the Examiner's initials in the left column next to each cited publication (except for JP 63-247656 in the May 25, 2001 Form PTO-1449).

On the copy of the May 25, 2001 Form PTO-1449 that was enclosed with the October 17, 2003 Office Action, the Examiner drew a line across JP 63-247656 and wrote "not present in application". It is respectfully requested that JP 63-247656 be considered and made of record, since JP 63-247656 was cited in the International Search Report that was enclosed with the INFORMATION DISCLOSURE STATEMENT filed on May 25, 2001.

The Examiner is thus requested to provide another copy of the Form PTO-1449 dated May 25, 2001 with the Examiner's initials in the left column next to each cited publication, including JP 63-247656.

The above amendments to the specification involve editorial revisions.

The amendments to claims 15 and 16 serve to correct minor clerical errors.

Applicants are pleased to note that claims 3, 6, 8 to 10 and 12 to 19 were considered to be allowable for the reasons set

forth in Item No. 5 on page 4 of the April 20, 2004 Office Action.

As recited in claim 1, the presently claimed invention concerns a method for quantitatively determining hydrogen sulfide or sulfide ions, which comprises adding to a sample containing hydrogen sulfide or sulfide ions, metal ions or a compound which liberates the metal ions and a metal indicator which reacts with the metal ions and resultingly undergoes color development, wherein the color development is accelerated or inhibited by the hydrogen sulfide or sulfide ions; and measuring the degree of color development of the metal indicator.

As recited in claim 4, the presently claimed invention is also directed to a method for quantitatively determining a specific substance, which comprises adding to a sample containing a specific substance, a component which acts on the specific substance so that the specific substance forms hydrogen sulfide or sulfide ions, metal ions or a compound which liberates the metal ions, and a metal indicator which reacts with the metal ions and resultingly undergoes color development, wherein the color development is accelerated or inhibited by the hydrogen sulfide or sulfide ions; and measuring the degree of color development of said metal indicator.

Claims 1, 2, 4 and 5 were rejected under 35 USC 102 as being anticipated by Dabovic USP 6,107,100 for the reasons set forth in

Item No. 2 on pages 2 and 3 of the April 20, 2004 Office Action.

The differences between the present invention and "Dabovic" are summarized in the following table.

	Present Invention	"Dabovic"
Object to be analyzed	thiol : no (In the case of homocysteine and cysteine, an enzyme produces hydrogen sulfide or sulfide ion.)	thiol : yes
	hydrogen sulfide or sulfide ion : yes	hydrogen sulfide or sulfide ion : no
Metal	Water soluble metal ion or metal-ion producing reagent	Water insoluble such as a basic Zn-slurry
Color Development	Metal indicator reacts with metal ion to form a colored metal-chelating complex.	Na-nitroprusside, which is not a metal indicator, reacts with thiols. A metal indicator is defined as a reagent having an ability to form a metal-chelating complex with a metal ion, whereas Na-nitroprusside (Na_2 [Fe (CN) $_5$NO] $2H_2O$) does not.
Result of Color development	Water soluble	Water insoluble
Measurement	The colored reaction mixture is ready for direct colorimetric measurement.	A filtration step or a solubilization (by EDTA) step is required for colorimetric measurement.

The object analyzed in the presently claimed invention is hydrogen sulfide and/or sulfide ion, but not a thiol-chemical. Since thiol-chemicals do not exhibit any effects on the assay system, a quantitative and specific determination of hydrogen sulfide and/or sulfide ion can be performed even in the presence of thiol-chemicals. In fact, the assay system in the presently claimed invention can include a thiol-chemical (2-mercaptoethanol with a concentration of 4 mM in the 1st reagent, and as a final 2.4 mM; see Examples 2-4 on pages 20 et seq. of the present specification) as a supplemental reagent. In contrast to the presently claimed invention, thiol-chemicals are the object analyzed in Dabovic.

In the presently claimed invention, the color development depends on the reaction in which a metal indicator reacts with metal ions to form a metal-chelating complex. In Dabovic, on the other hand, Na-nitroprusside, which does not react with metal ions, but rather reacts with thiol-residues, is the object to be measured. The chemical formula of Na-nitroprusside is $Na_2[Fe(CN)_5NO]2H_2O$, in which a metal element, namely Fe, is contained. Despite the existence of the metal element Fe, Na-nitroprusside itself does not develop color, and also it has not been shown that it exhibits any specificity to react with metal ions. So, it is generally not categorized as a metal indicator. See the following

definition of a metal indicator which the applicants have provided:

''Metal indicator, metallochromic indicator'': A metal chelating reagent, which is utilized for determining the final equivalence point of titration of metal ion M in a solution. In such reaction, which is indicated hereinbelow, metal chelating reagent X that acts as an indicator is pre-added to a metal ion-containing solution to form MX having a color, for example, red, and then the solution is titrated with the other metal chelating reagent Y, which removes M out from MX to produce coloring component MY (having a color, for example, blue, which is different from that of MX), resulting in a dynamic color change of the reaction mixture, and visually indicating the equilibrium point.

MX (color red for example) + Y $\Leftrightarrow$ MY (color blue for example) + X

Further, in Dabovic, color is developed in conjunction with a water insoluble compound such as a Zn-slurry, which leads to an assay system which is inconvenient for a direct measurement in a liquid solution because of the filtration- or solubilization (by EDTA)- step required for a colorimetric measurement. In contrast to Dabovic, in the presently claimed invention, the colored reaction mixture constituted by a metal, a metal indicator, and the resulting metal-chelating complex, which are all water soluble, and ready for

direct colorimetric measurement in the liquid solution.

The following positions were set forth in the paragraph bridging pages 3 and 4 of the Office Action:

(a) "the Examiner's position that the quantitative determination of hydrogen sulfide and/or sulfide ions is inherent in Dabovic's invention"

(b) "As a result of the reduction of disulfides to the thiol state, sulfide ions are released."

Applicants respectfully rebut the above positions based on the following reasons:

Regarding (a) above, although Na-nitroprusside itself is known to be a chemical which could be utilized in a quantitative determination of sulfide ions, the principle of applicants' claimed method is different from that of Dabovic's where a basic Zn-slurry is necessitated. In fact, in Photo 7 of Dabovic, the thiol-chemicals (shown in 2-5) develop colors clearly in 200 μM, while Na_2S (sodium sulfide)(shown in 8) does not, which is relatively at a level of negative control water (shown in 1).

Concerning (b) above, in "Dabovic", TCEP, tris(2-carboxyethyl) phosphine, is utilized as a reducing reagent to transform disulfide into thiols, as depicted in the following reaction:

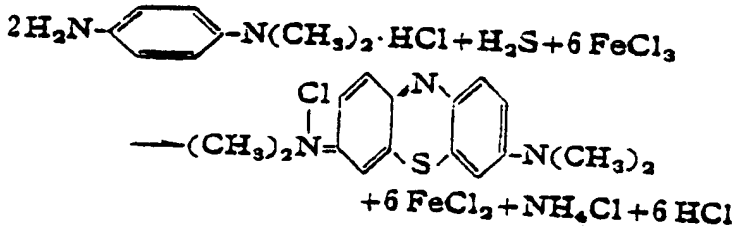
$$R'_3P + RSSR + H_2O \rightarrow R'_3P{=}O + 2RSH$$

As shown above, the reaction does not produce sulfide ions.

Claims 7 and 11 were rejected under 35 USC 102 as being anticipated by Tan et al. USP 5,985,540 for the reasons set forth in Item No. 3 of the Office Action.

Regarding Tan et al., the principle that the present invention depends on is different from that of Tan et al., for the following reasons.

In Tan et al., N,N-dimethyl-p-phenylenediamine ("NDPD") is oxidized by $FeCl_3$ to become methylene blue, which incorporates the element S derived from hydrogen sulfide. The well-known reaction is illustrated as follows:



NDPD does not react with the metal Fe, so as not to form a colored metal chelating complex. Thus, NDPD is not categorized as a metal indicator (see the above definition of a metal indicator). Furthermore, the reaction system producing methylene blue is necessitated by being performed in a very low pH, namely an acidic condition, which is in contrast to the present invention where the

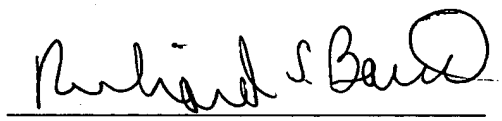
reaction system can be performed in a natural or weak alkali.

It is therefore respectfully submitted that applicants' claimed invention patentably distinguishes over the references.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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